Three arterial grafts improve late survival:

a meta-analysis of propensity matched studies

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Abstract

Background: There is little evidence whether a third arterial graft provides superior outcomes in comparison to the use of two arterial grafts in patients undergoing coronary artery bypass grafting (CABG). A meta-analysis of all the propensity score matched (PSM) observational studies comparing the long-term outcomes of CABG with the use of two (2-ART) vs. three arterial (3-ART) grafts was performed.

Methods: A literature search was conducted using MEDLINE, EMBASE, and Web of Science to identify relevant articles. Long-term mortality in the PSM populations was the primary endpoint. Secondary endpoints were in-hospital/30-day mortality for the PSM populations and long-term mortality for the unmatched populations. In the matched population, time-to-event outcome for long-term mortality was extracted as hazard ratios (HRs) along with their variance. Statistical pooling of survival (time-to-event) was performed according to a random effect model, computing risk estimates with 95% confidence intervals (CI).

Results: A total of 8 PSM studies reporting on 10,287 matched patients (2-ART: 5346; 3-ART: 4941) were selected for final comparison. The mean follow-up time ranged from 37.2 to 196.8 months. The use of three arterial grafts was not statistically associated with early mortality (HR, 0.93; 95% CI, 0.71-1.22; p= .62). The use of three arterial grafts was associated with statistically significantly lower hazard for late death (HR, 0.8; 95% CI, 0.75-0.87; p< .001), irrespective of sex and diabetic status. This result was qualitatively similar in the unmatched population (HR, 0.57; 95% CI, 0.33-0.98; p= .04).

Conclusions: The use of a third arterial conduit in CABG patients is not associated with higher operative risk and is associated with superior long-term survival, irrespective of sex and diabetic status.

Clinical Perspective

What is new?

- The best available evidence suggests that the use of a second arterial graft at the time of coronary artery bypass operations leads to better postoperative survival.
- However, less is known about the potential benefit of a third arterial conduit.
- In the present analysis, we show that adding a third arterial conduit is not associated with an increased operative risk and is associated with improved long-term survival.

What are the clinical implications?

- Arterial grafts are largely underused for coronary artery bypass surgery.
- By showing an association between improved survival and the use of a third arterial graft, these results support such a strategy and provide support for consideration of evaluation and confirmation in prospective randomized trials.

Introduction

Current observational evidence strongly suggests that the use of two arterial grafts at the time of coronary artery bypass surgery (CABG) is associated with long-term survival benefits[1-3]. However, less is known about the potential benefit of a third arterial conduit.

To date, the studies that have compared the long-term survival of CABG patients receiving two vs. three arterial conduits have reported conflicting results[4-11]. However, all of these studies come from single centers and have limited sample size. It is highly likely that the potential additional survival benefit of a third arterial conduit is less when compared to that of a second, making it plausible that single institutional studies are underpowered to detect moderate differences in survival.

In order to overcome this limitation and to provide the best available evidence on this topic, we present a meta-analysis of propensity score matched (PSM) observational studies that compared the long-term outcomes of CABG in patients who received two vs. three arterial grafts.

Methods

Search Strategy and Selection of Studies

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12].

In August 2016, a literature search using MEDLINE, EMBASE, and Web of Science to identify relevant articles was performed. Observational studies included in the present meta-analysis met the following criteria: (1) patients undergoing first time isolated CABG; (2) comparison of long-term survival of patients receiving two arterial conduits (2-ART) vs. patients receiving three arterial conduits (3-ART); and (3) PSM was used to account for non-random allocation to treatment (2-ART vs. 3-ART). Non-English language, review articles, case reports, and editorials were excluded. Search terms used the controlled vocabularies of MEDLINE and EMBASE alone or in combination with text words including ‘‘third arterial conduit CABG’’, “third arterial graft CABG’’, ‘‘total arterial revascularization CABG’’, ‘‘propensity score’’, and ‘‘propensity score matching’’. Two reviewers (M.G. and A.D.F.) independently reviewed the titles and abstracts to determine whether the study met the inclusion criteria. In the case of disagreement, an agreement was negotiated. In the case of several publications with overlapping study populations, the largest sample size study with longest follow-up available was selected.

We assessed the quality of included studies with the Newcastle-Ottawa Scale for observational studies[13]. The highest possible score is 9 stars, and the quality is graded as low level (<6 stars) or high level (≥6 stars).

Data Extraction

Microsoft Office Excel 2010 (Microsoft, Redmond, Wash) was used for data extraction that was performed independently by 2 researchers (A.D.F. and L.B.O.). In the case of initial disagreement, an agreement was negotiated. Where additional information was deemed necessary, the corresponding author of the relevant study was contacted directly. Study design, study period, country, and center where the study was conducted, unmatched and matched sample size, type of arterial conduits, PSM methods, completeness of follow-up, and follow-up duration were documented. The following patient characteristics in the unmatched and matched groups were also registered: age, female sex, diabetes mellitus, reduced left ventricular ejection fraction (as defined by the authors), chronic obstructive pulmonary disease, renal impairment (as defined by the authors), target vessels, and predicted operative risk according to the EuroSCORE or the Society of Thoracic Surgeons score[14].

The primary endpoint was long-term mortality in the matched populations. Secondary endpoints were in-hospital/30-day mortality for the matched populations and long-term mortality in the unmatched populations. In the matched population, time-to-event outcome for long-term mortality was extracted as hazard ratios (HRs) along with their variance.

Statistical Analysis

Continuous variables are reported as median (25th, 75th percentile) or as mean±standard deviation. Categorical variables are expressed as (%). Statistical pooling of survival, time-to-event, was performed according to a random-effect model, computing risk estimates with 95% confidence intervals (CI), using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane

Centre and Copenhagen, Denmark). From one study we derived the incidence of all-cause mortality from a Kaplan-Meier survival curve using a described method[15]. Study bias was appraised by graphical inspection of funnel plots, and Egger's linear regression method was used to quantify the bias. Hypothesis testing for equivalence was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and was based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively. Meta-regression analysis and the "one study removed analysis" were performed with Comprehensive Meta-Analysis, reporting results as regression coefficient (i.e. Beta).

Results

Selected Studies

From 201 abstracts, 21 full-text articles fitting the relevant selection criteria were selected. After evaluating the full-text articles, 13 observational studies that did not perform PSM adjusted comparison between patients receiving two vs three arterial conduits[16-28] were excluded. A total of 8 PSM studies were finally selected for the systematic review and meta-analysis[4-11]. An outline of the systematic review process is depicted in Figure 1. An overview of the PSM studies is summarized in Tables 1 and 2 (variables included for PSM are summarized in Supplementary Table 1). Overall, selected studies reported on 10,287 matched patients (2-ART, 5346; 3-ART, 4941) for final comparisons. PSM populations presented a similar preoperative risk factor distribution in the 2-ART and 3-ART groups (Table 3).

Early Mortality

All studies except for three[5,6,8] reported on comparisons of in-hospital/30-day mortality for the PSM series (different definitions were adopted, see Table 1). Glineur et al. did not report any data on in-hospital/30-day mortality and two other studies, Locker et al. and Di Mauro et al., reported overall mortality without distinguishing between the 2-ART and 3-ART groups. In-hospital/30-day mortality ranged from 0.4% to 2.7% and 0.3% to 2.9% in the 2-ART and 3-ART groups, respectively. Pooled estimates showed no significant difference between the two groups (HR: 0.93; 95% CI, 0.71-1.22; p= .62; Figure 2). Meta-regression analysis showed neither female sex (Beta -0.13 [CI -0.02; +1.75], p= .89) nor diabetes affected early outcome (Beta -0.14 [CI -1-47; +1.19], p= .83).

Long-Term Mortality

All studies reported the comparison of long-term mortality for the PSM series. However, Nasso et al.[10] reported survival in a Kaplan Meier survival curve. In this study the HR for long-term mortality was then derived from the Kaplan Meier as described in the Methods section. In the study by Di Mauro et al.[5] the HR for the 2-ART and 3-ART groups could not be calculated and this study was omitted from the final analysis.

The mean follow-up time ranged from 37.2 to 196.8 months (Table 2). The use of three arterial grafts was associated with a statistically significant reduction of late death when compared with the use of two arterial conduits (HR: 0.8; 95%CI, 0.75-0.87; p< .001; Figure 3). This result was confirmed in the studies[4,6,8,11] that reported the late mortality in the unmatched population (HR: 0.57; 95% CI, 0.33-0.98; p= .04; Figure 4). The leave-one-out analysis confirmed these results (Figure 5).

Meta-regression analysis showed neither female sex (Beta 0.13 [-0.23; +0.5), p= .47) nor diabetes affected long-term survival (Beta 0.19 [CI -0.23; +0.64], p= .4).

Publication Bias and internal validity appraisal

The Newcastle-Ottawa Scale confirmed a high-quality level for all PSM studies included in the main analysis (Supplementary Table 2). Heterogeneity for PSM analysis was high for long-term (I^2= 58.8%) and for 30-day mortality (I^2= 85.6%), and extensive in the overall population analysis (I^2= 91.3%). No significant publication bias was found, as confirmed by Egger's test (Supplementary Figures 1 and 2).

Discussion

Even in the absence of randomized controlled trials (RCTs), the clinical benefits related to the use of two arterial grafts at the time of CABG are strongly supported by abundant circumstantial evidence. In 1999 the Cleveland Clinic investigators were among the first to report a clear survival advantage for patients receiving bilateral internal thoracic artery (BITA) instead of single internal thoracic artery (SITA) grafts[29]. Since that seminal paper, a substantial amount of observational evidence has reported better clinical outcomes with the use of two vs. one arterial grafts for CABG patients.

Most recently, the 5-year interim analysis of the ART trial that randomized 3,102 patients to receive SITA or BITA showed similar mortality, myocardial infraction and stroke[30]. There are several possible explanations for the similar outcomes. First, the failure rate of saphenous vein is known to be relatively low for the first 5 years after CABG but then increases. Second, very high use of guideline based medical therapy with almost 90% of the patients receiving aspirin and statins and almost three quarters on beta-blockers and ACE inhibitors, may have reduced the risk of development of disease and failure of vein grafts. Third, the simultaneous use of a radial artery (with its proven superior angiographic patency in comparison to vein grafts at 5 years[31]) in 20% of the SITA group may also have resulted in a narrowing of differences in mid-term outcome. A further possibility is that while the addition of a second ITA graft makes no difference to 5-year survival, this may change over the longer-term as there is a marked difference in angiographic patency between ITA and vein grafts after 10 years[32].

While awaiting the 10-year outcomes of ART, current available evidence suggests that the use of two arterial grafts for CABG is associated with significantly better outcome. Indeed, in a meta-analysis of over 15,000 patients receiving SITA or BITA followed for a mean of over 9 years, the Oxford group reported a 22% survival benefit for those receiving two arterial conduits (HR: 0.78; CI, 0.72–0.84; p< .0001)[33]. Similarly, in the only meta-analysis that compared clinical outcomes of patients receiving either a radial artery or a saphenous vein as the second graft, Zhang and coauthors found a significantly lower incidence of cardiac death, myocardial infarction, and repeat coronary procedures in the arterial group (OR: 0.72, 0.68, and 0.27 respectively)[34].

The benefits related to the addition of a third arterial conduit are much more controversial. The few studies that have directly compared the outcomes of patients receiving two vs. three arterial grafts have reported conflicting results. Di Mauro et al., analyzing a cohort of 885 patients with BITA to the left coronary artery system, described increased mortality and cardiac-death rates when the gastroepiploic artery instead of the saphenous vein was used to graft the right coronary artery[5]. Similarly, Nasso and associates found no additional clinical benefits with the addition of a third arterial graft in a large cohort of 10,752 CABG patients[10]. In addition, Benedetto et al. and Mohammadi et al. found that using the radial artery or the saphenous vein in addition to BITA did not improve long-term outcomes[4,9].

On the other hand, the Mayo Clinic group reported improved late survival with the use of three arterial conduits[8] and Glineur et al. had superior outcomes using the gastroepiploic artery, instead of a saphenous vein, to complement the two ITAs[6]. Both Grau and Shi and coauthors, in two large propensity matched series, reported a significant survival benefit for patients who received three vs. two arterial conduits[7,11].

One possible reason for these contradictory findings is that the survival benefit provided by the use of a third arterial graft is lower when compared to the use of the first or second arterial conduit. Consequently, in view of their relatively small individual populations, most of the single institutional studies were underpowered to detect moderate differences in survival. The present study was meant to overcome this potential limitation by using a meta-analytic approach.

Even though meta-analyses of PSM studies are not as methodologically robust as meta-analyses of RCTs, they are emerging as an attractive alternative. In view of the paucity of evidence from RCTs in the surgical literature, the meta-analytic approach based on PSM studies can be relied on as evidence when RCTs are not possible or not available[35].

Our analysis pooled data from 10,287 matched patients receiving two vs. three arterial conduits. Our main finding is that the use of a third arterial graft is not associated with an increase in the operative risk but rather with a 24% survival benefit at a mean follow-up of 77.9 months. This survival advantage is independent of the patient's sex and diabetic status.

The most likely explanation for these findings is the demonstrated lower attrition rate of arterial grafts. All the studies that have compared the angiographic patency of arterial vs. venous bypass grafts have consistently shown a better patency rate for the former, with the difference in patency increasing with the length of the follow-up[31,36].

Indeed, we have recently described how 20 years after CABG the risk of graft failure for the venous grafts is almost three times higher than that of arterial conduits[32]. An additional potential contributor to the improved outcomes of patients who received three arteries is probably the protective effect of arterial grafts against the development of atherosclerotic disease in the native coronary circulation[37].

Unfortunately, the available data do not allow a further analysis of eventual survival differences related to the location of the third arterial conduit on the left or right coronary system or the type of graft configuration used. These are important points that require further investigation.

It is important to note that in the US only 6% of the patients undergoing primary isolated CABG receive more than one arterial graft[38]. A similar situation exists in Europe and in Asia[38,39]. Even in the absence of global data, the current literature suggests that the proportion of patients receiving a second arterial conduit at the time of CABG worldwide is in the 15-20% range.

The reasons for this underuse of arterial grafts are complex and multifactorial. The increasing complexity of the population of patients referred for CABG, but also the increasing pressure toward higher surgical "productivity" and the importance of short-term "quality metrics", such as the avoidance of sternal complications, are possible explanations.

Limitations

The present analysis has intrinsic limitations. First, any matching system can only adjust for measurable and included variables. It is likely that while selecting which patients should receive three arterial grafts the operating surgeons relied on an immeasurable, but reliable, "eyeballing" that comes from experience and cannot be neutralized by any statistical method. This means that healthier patients are more likely to have received three arterial conduits.

Secondly, propensity matching by definition increases internal validity at the expense of generalizability. The fact that only about two thirds of the overall population was included in the matched comparison clearly limits the ability to extend our findings to the majority of CABG patients.

Also, looking at Table 3, it is evident that the population of patients included in most of the examined studies is younger and in general healthier than that seen by most cardiac surgery centers in their everyday clinical practice. It is highly likely that this patients' population represents a selected group of the totality of cases referred for CABG and it is possible that the described benefits associated with the use of a third arterial grafts does not apply to the generality of the CABG population.

Moreover, not all the studies evaluated all the outcomes of interest, so we specified the number of the studies and of patients for each outcome; most of the results are based on very small numbers of deaths. Group level analysis also introduced the problem of ecological bias for regression of ecologic variables such as sex or diabetes, potentially failing to detect these interactions[40].

Finally, the different authors used different grafting strategies and matching models so that the homogeneity of the included populations cannot be regarded as optimal.

In conclusion, in a meta-analysis of the PSM studies comparing the use of two vs. three arterial grafts for CABG, we found that the use of three arterial conduits is not associated with an increase in the operative risk but is associated with a statistically significant survival benefit at long-term follow-up. These finding support the concepts that complete revascularization and extensive use of arterial grafts should be the cornerstone of modern coronary artery surgery.

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Figure Legends

Figure 1. Flow chart for study selection.

Figure 2. Forest plot comparing the effect of the use of three arterial conduits (3-ART) vs. two arterial conduits (2-ART) on in-hospital/30-day mortality across individual propensity score-matched studies. CI, confidence interval (5 studies including 9106 patients).

Figure 3. Forest plot comparing the effect of the use of three arterial conduits (3-ART) vs. two arterial conduits (2-ART) on late mortality across individual propensity score-matched studies. CI, confidence interval. (7 studies including 9402 patients).

Figure 4. Forest plot comparing the effect of the use of three arterial conduits (3-ART) vs. two arterial conduits (2-ART) on late mortality across individual unmatched studies. CI, confidence interval. (4 studies including 3742 patients).

Figure 5. Forest plot of the leave-one-out analysis comparing the effect of the use of three arterial conduits (3-ART) vs. two arterial conduits (2-ART) on late mortality. CI, confidence interval.

Supplementay Figure 1. Funnel plot comparing the effect of the use of three arterial conduits (3-ART) vs. two arterial conduits (2-ART) on late mortality across individual propensity score-matched studies.

Supplementay Figure 2. Funnel plot comparing the effect of the use of three arterial conduits (3-ART) vs. two arterial conduits (2-ART) on in-hospital/30-day mortality across individual propensity score-matched studies.

Table 1. Overview of propensity score-matching studies included in the primary analysis

Study	Year	Country	Centers	Study period	Conduits 2-ART	Conduits 3-ART	PSM Methodology	SV target (2-ART UNM)	Outcomes of interest reported (PSM populations)
Benedetto[4]	2016	United Kingdom	Bristol Heart Institute	1996- 2015	BITA-GSV	BITA-RA	Greedy 1:1 matching with caliber width of 0.2 SD	CX, DIA, RCA	In-hospital mortality. All-cause late mortality.
Di Mauro[5]	2008	Italy	University of Chieti	1991- 2002	BITA-GSV	BITA-RA BITA-RGEA	2:1 matching method not reported	RCA	Long-term death from any cause.
Glineur[6]	2013	Belgium	Cliniques Universitaire St Luc, Brussels	1985- 1995	BITA-GSV	BITA-RGEA	Matching method not reported	RCA	Overall survival.
Grau[7]	2015	United States	The Valley Columbia Heart Center, Ridgewood, NJ. University of Pennsylvania, Philadelphia, PA	2000-2013	BITA-GSV	BITA-RA	Greedy 1:1, 5-1 digit matching	CX, LAD, RCA	30-day mortality. Long-term survival.
Locker[8]	2012	United States	Mayo Clinic, Rochester, MN	1993- 2009	BITA-GSV	BITA-RA	1:1 matching method not reported	CX, DIA, RCA	Late death: after 30 days.

Mohammadi[9]	2016	Canada	Quebec Heart and Lung University Institute, Quebec City, Quebec	1991- 2013	BITA-GSV	BITA-RA	5-digit 1:1 matching without replacement	CX, RCA	Short-term (in-hospital) mortality. Long-term all-cause mortality.
Nasso[10]	2012	Italy	Anthea Hospital, GVM Care & Research, Bari	2003-2008	BITA-GSV	BITA-RA	1:1 matching nearest-neighbor matching caliber width of ± 0.1	CX, RCA	Operative death: within 30 days of the operation or before hospital discharge). Long-term mortality.
Shi[11]	2016	Australia	St. Vincent's Hospital, University of Melbourne, Melbourn	1995- 2010	BITA-GSV	BITA-RA	Greedy 1:1 matching with fixed caliber width of 0.05 without replacement	CX, RCA	Short-term (30-day) mortality. Long-term survival.

BITA, bilateral internal thoracic arteries; CX, circumflex coronary system; DIA, diagonal coronary artery; GSV, greater saphenous vein; LAD, left anterior descending artery; PSM, propensity score-matched; RA, radial artery; RCA, right coronary artery; RGEA, Right gastroepiploic artery; UNM, unmatched.

Table 2. Overview of propensity score-matching studies included in the primary analysis.

Study	Overall population, n	UNM 2-ART, n	UNM 3-ART, n	PSM 2-ART, n	PSM 3-ART, n	Mean/median follow-up (months)	Completeness of follow-up (%)	PSM-HR for long-term mortality provided
Benedetto[4]	764	489	275	275	275	2-ART= 126 ± 58.8 3-ART= 126 ± 54	100	Yes
Di Mauro[5]	1015	643	372	590	295	2-ART= 88 3-ART= 128	100	No
Glineur[6]	297	204	93	203	93	2-ART= 196.8 ± 74.4 3-ART= 192 ± 64.8	NR	Yes
Grau[7]	751	568	183	183	183	NR (max 14 years)	100	Yes
Locker[8]	1184	1029	155	NR	NR	Mean: 91.2 ± 55.2 Median: 87.6	94	No
Mohammadi[9]	1750	1495	255	249	249	2-ART= 97.8 (IQR, 0.03- 22.6) 3-ART=97.2 (IQR, 0.02-17)	100	Yes
Nasso[10]	7767	NR	NR	3584	3584	Mean: 37.2	98	No
Shi[11]	1497	460	1037	262	262	2-ART= 144 ± 60 3-ART= 144 ± 60	100	No

ART, arteries; HR, hazard ratio; IQR, inter-quartile range; NR, not reported; PSM, propensity score-matched; UNM, unmatched.

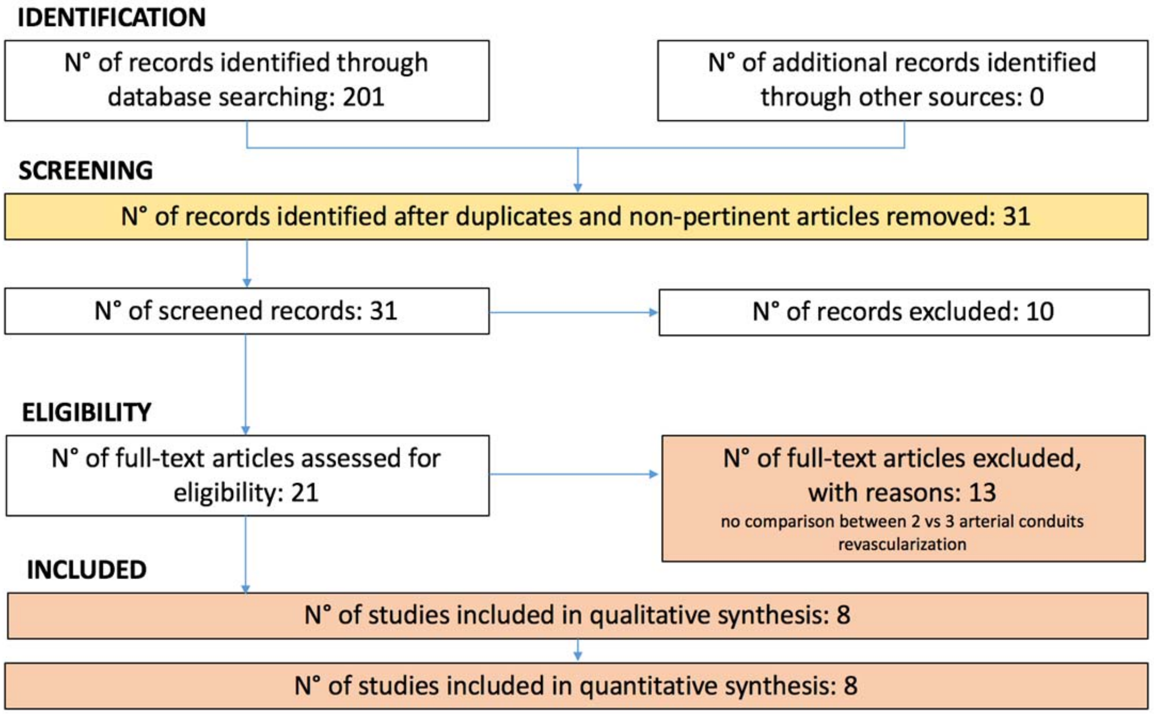
Table 3. Risk factor distribution in the matched populations in studies included in the primary analysis.

	Matched							
Study	**Age (y) Mean±SD**	**Female (%)**	**DM (%)**	**EF (%)**	**COPD (%)**	**CRF (%)**	**STS score (%)**	**EuroSCORE (%)**
Benedetto[4]								
2-ART	NR	5.8	5.5	NR	2.5	0.7	NR	NR
3-ART	NR	6.5	6.5	NR	2.9	0.4	NR	NR
Di Mauro[5]								
2-ART	62.6 ± 8.7	12.5	21.4	60.6 ± 12.8	5.1	0	NR	3.5 ± 2.9
3-ART	62.1 ± 8.0	11.9	20.7	59.5 ± 12.0	4.4	0.3	NR	3.1 ± 2.8
Glineur[6]								
2-ART	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)
3-ART	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)	NR (quintiles)
Grau[7]								
2-ART	58 ± 9	6.6	5.5	53 ± 11	2.2	0	0.8	NR
3-ART	57 ± 10	7.7	6.0	52 ± 10	2.7	0	0.8	NR
Locker[8]								
2-ART	NR	NR	NR	NR	NR	NR	NR	NR
3-ART	NR	NR	NR	NR	NR	NR	NR	NR
Mohammadi[9]								
2-ART	55.8±8.9	11.2	13.7	57.9±12.8	6.8	1.6	11.2	11.2

3-ART	56.1±8.9	9.6	12.1	59.9±12.5	4.4	2.4	9.6	9.6
Nasso[10]								
2-ART	67.3 ± 9.3	20.4	48.2	NR (ranges)	9.9	NR	NR	NR (ranges)
3-ART	67.1 ± 9	20.1	48.0	NR (ranges)	10.0	NR	NR	NR (ranges)
Shi[11]								
2-ART	NR (ranges)	9	13	NR (ranges)	NR	0	NR	NR
3-ART	NR (ranges)	10	13	NR (ranges)	NR	1	NR	NR

COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure (different definitions adopted); DM, diabetes mellitus; EF, ejection fraction; NR, not reported; SD, standard deviation; STS, Society of Thoracic Surgeons score.

Figure 1.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N° of additional records identified through other sources: 0
SCREENING
N° of records identified after duplicates and non-pertinent articles removed: 31
N° of screened records: 31
N° of records excluded: 10
ELIGIBILITY
N° of full-text articles assessed for eligibility: 21
N° of full-text articles excluded, with reasons: 13
no comparison between 2 vs 3 arterial conduits revascularization
INCLUDED
N° of studies included in qualitative synthesis: 8
N° of studies included in quantitative synthesis: 8

Figure 2.

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Hazard ratio and 95% CI	Relative weight
Benedetto	2,01	0,18	22,36	0,57	0,57		1,25
Grau	0,49	0,05	5,15	-0,59	0,55		1,31
Mohammadi	0,49	0,05	5,15	-0,59	0,55		1,31
Nasso	0,94	0,71	1,24	-0,43	0,66		93,25
Shi	1,00	0,20	4,88	0,00	1,00		2,88
Overall	0,93	0,71	1,22	-0,49	0,62		

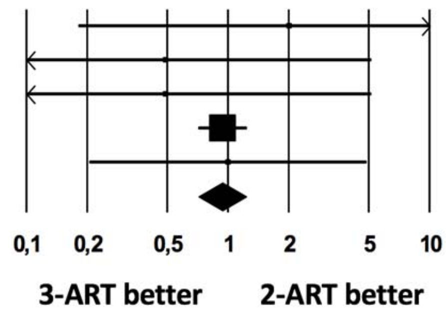

Figure 3.

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Benedetto	1,16	0,71	1,90	0,59	0,56	2,22
Glineur	0,41	0,22	0,75	-2,88	0,00	1,48
Grau	0,25	0,06	1,01	-1,95	0,05	0,28
Locker	0,73	0,59	0,90	-2,92	0,00	12,22
Mohammadi	0,90	0,40	2,01	-0,26	0,80	0,84
Shi	0,87	0,79	0,96	-2,80	0,01	57,35
Nasso	0,72	0,62	0,83	-4,41	0,00	25,60
Overall	0,80	0,75	0,87	-5,77	0,00	

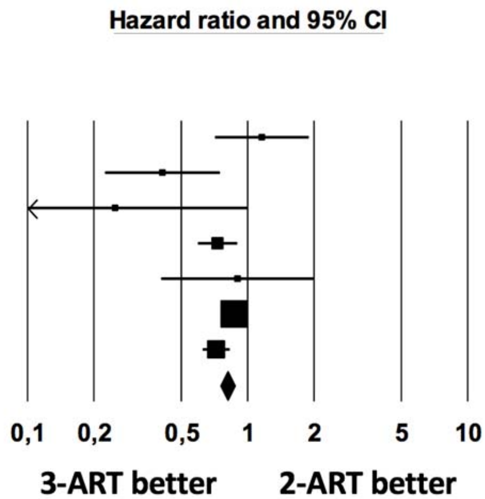

Figure 4.

Study name	Statistics for each study					Relative weight
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	
Benedetto	1,27	0,79	2,04	0,99	0,32	23,73
Glineur	0,46	0,25	0,85	-2,46	0,01	21,11
Locker	0,33	0,28	0,39	-13,12	0,00	28,14
Shi	0,58	0,44	0,76	-4,00	0,00	27,03
Overall	0,57	0,33	0,98	-2,03	0,04	

Hazard ratio and 95% CI

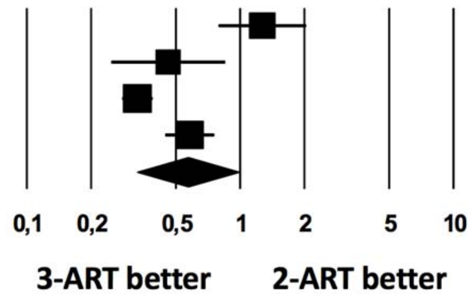

Figure 5.

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Benedetto	0,737	0,621	0,876	-3,474	0,001
Glineur	0,797	0,688	0,923	-3,027	0,002
Grau	0,778	0,664	0,913	-3,087	0,002
Locker	0,769	0,620	0,953	-2,401	0,016
Mohammadi	0,758	0,633	0,907	-3,026	0,002
Nasso	0,771	0,611	0,972	-2,200	0,028
Shi	0,722	0,583	0,894	-2,987	0,003
	0,765	0,646	0,906	-3,109	0,002

Overall